

Statistical Analysis Plan

Study Protocol Number: SARPAC

Study Title:

**A prospective, randomized, open-label, interventional study to
investigate the efficacy of sargramostim (Leukine®) in
improving oxygenation and short- and long-term outcome of
COVID-19 patients with acute hypoxic respiratory failure.**

Study Sponsor:

University Hospital Ghent.

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1 Signature Page

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Approval

The undersigned have reviewed and approved the Statistical Analysis Plan and find the document to be consistent with the requirements of the Protocol.

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2 Amendment/Modification History

The following table documents any changes made to the previously approved versions of the document.

Version #	Page # / Section	Summary of Changes	Date
1.0	Original	NA	xx-xxx-2020

3 Abbreviations

AE :	Adverse Event
AECC :	American-European Consensus Conference
ALT:	Alanine Aminotransferase
ARDS :	Acute Respiratory Distress Syndrome
AST:	Alanine Aminotransferase
CK:	Creatine Kinase
COVID-19 :	Coronavirus induced disease-2019
CRP:	C-reactive protein
DSMB :	Data Safety Monitoring Board
ECG :	Electrocardiogram
ESR:	Erythrocyte Sedimentation Rate
eCRF :	electronic Case Report Form
FiO ₂ :	Fraction of inspired oxygen
FVC :	Forced vital capacity
GM-CSF :	Granulocyte-macrophage colony stimulating factor
ICF :	Informed Consent Form
ICU:	Intensive Care Unit
LDH:	Lactate Dehydrogenase
PaO ₂ :	Partial pressure of oxygen
SAE :	Serious Adverse Event
SUSAR :	Suspected Unexpected Serious Adverse Reaction
TLC :	Total Lung Capacity
WBC:	White Blood Cells

4 Introduction

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methodologies that will be used in the analysis and reporting of results for Protocol SARPAC.

This document is prepared based on the following documents:

- the study protocol version 3.0 dated 14 May 2020;
- the Case Report Form version 2.0 dated 08 April 2020.

Readers are referred to the final study protocol (and any amendments or addenda), the case report form (CRF), and CRF completion guidelines for details of the study design, conduct and data collection. Any significant changes to these documents in terms of the principle features of the study analyses may result in a SAP amendment; any other changes will be denoted in the Clinical Study Report as changes to the planned analyses.

This SAP must be finalized prior to the locking of the clinical database for this study. The mock summary tables, figures and by subject data listings (TFLs) are provided in a separate document.

5 Study Objectives and Endpoints

5.1 Primary Objective

The primary objective is to investigate whether the administration of sargramostim (Leukine®) improves oxygenation and short and long-term outcomes in COVID-19 patients with acute hypoxic respiratory failure.

5.1.1 Primary Endpoint

To measure the effectiveness of sargramostim on restoring lung homeostasis, the primary endpoint of this intervention is measuring oxygenation after 5 DAYS of inhaled (and intravenous) treatment through assessment of pretreatment (day 1) and post-treatment (day 6) ratio of PaO₂/FiO₂ and through measurement of the P(A-a)O₂ gradient.

During the 5 day treatment period, daily measurements of oxygen saturation (pulse oximetry) in relation to FiO₂ will be performed, and the slope of alterations in this parameters could also be an indicator of correctness of study hypothesis.

The post-treatment evaluations should be assessed within 24 hours of the last dose of treatment. That is, Day 6 will be the timepoint for measures of efficacy endpoints based on 5 days of treatment, and Day 10 for patients who complete 10 days of treatment. If the patient is discharged from hospital prior to the day 6 (or day 10) efficacy evaluations, the values at day of discharge will be used as value for measuring efficacy endpoints.

5.1.2 Secondary Objectives & Endpoints

- to study if early intervention with sargramostim is safe (number of AEs/SAEs)
 - Incidence of AEs/SAEs.
- to study if early intervention with inhaled sargramostim affects clinical outcome
 - Length of hospital stay.
 - Mean change in 6-point ordinal scale between day 1 and day 6.
 - Mean change in clinical sign score between day 1 and day 6.
 - Time to clinical sign score < 6 maintained for 24h.
 - Mean change of SOFA score between day 1 and day 6 or between day 1 and day 10.
 - Mean change NEWS2 score between day 1 and day 6 or between day 1 and day 10.
 - Time to NEWS2 score less than 2 for at least 24h.
- to study if early intervention with sargramostim affects the rate of nosocomial infection
 - Rate of nosocomial infection.
- to study if early intervention with inhaled sargramostim affects progression to mechanical ventilation and/or ARDS
 - Number of patients requiring initiation of mechanical ventilation.
 - Duration of invasive and non-invasive ventilation and/or supplemental oxygen.
- to study if treatment with sargramostim affects all cause mortality rate at 20 weeks post inclusion
 - All-cause mortality rate at 4 and 20 weeks post inclusion.
- to study if treatment with sargramostim affects features of secondary haemophagocytic lymphohistiocytosis, as defined by Hs score (temp, organomegaly, cytopenia, triglycerides, fibrinogen, ferritin, AST and known immunosuppression)

- Features of secondary haemophagocytic lymphohistiocytosis.
- to study if treatment with sargramostim has a favourable effect on long term 10-20 week follow up
 - Clinical exams performed at 10-20 weeks follow up.
 - Pulmonary function tests (including FVC, TLC and diffusion capacity) performed at 10-20 weeks follow up.
 - Laboratory tests (ferritin, lymphocytes, leukocytes) performed at 10-20 weeks follow up.

6 Study Design

6.1 Study Design Overview

This is phase 4 academic, prospective, randomized, open-label, interventional study designed to investigate the efficacy of sargramostim (Leukine®) in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure.

Patients with confirmed COVID19 with acute hypoxic respiratory failure (saturation below 93% on minimal 2 l/min O2 or PaO2/FiO2 <350) will be randomized to receive sargramostim 125mcg twice daily for 5 days as a nebulized inhalation on top of standard of care (active group), or to receive standard of care treatment (control group). Upon progression of disease to requiring initiation of non-invasive or invasive mechanical ventilatory support within the 5 day period, in patients in the active group, inhaled sargramostim will be replaced by intravenous sargramostim 125mcg/m2 body surface area until the 5 day period is reached.

The number of subjects that will be included in this study is: 80.

These are divided into following sub-groups:

Group A: active sargramostim treatment group, treatment for initial 5 days, no deterioration after 5 days

Number of patients : 40

Group B: control group : no treatment with sargramostim in first 5 days

Number of patients : 40

Group C and D:

From day 6 onwards, progressive patients in the active group (Group A) will have the option to receive an additional 5 days of IV sargramostim 125mcg/m² body surface area once daily, based on the treating physician's assessment. This group will be called group C. It is estimated that some 30% of patients might deteriorate and require noninvasive or invasive mechanical ventilation, resulting potentially in 12 patients that progress from group A to group C, if the clinician decides to move forward with the drug.

In the control group (Group B) progressing to requiring invasive or non-invasive mechanical ventilatory support, from day 6 onwards, the treating physician will have the option to initiate IV sargramostim 125mcg/m² body surface area once daily for 5 days. This group will be called group D. It is estimated that some 30% of patients might deteriorate to mechanical ventilation or ARDS, resulting potentially in 12 patients that progress from group B to group D, if the clinician decides to move forward with the drug.

Comparisons between group A (early sargramostim) versus group B (no sargramostim) at day 6 will be important for reaching primary endpoint, and for key secondary endpoints. Comparisons of Group A (early 5 day intervention with sargramostim) with Group D (late 5 day intervention with sargramostim) will also be very informative for secondary endpoint analysis.

Refer to Section 5.1 of the Study Protocol for a more detailed description of the study. Section 1.6.2 of the Study Protocol is a schematic of the study design.

6.2 Randomization

In this open label trial patients will be randomized in a 1:1 ratio. Randomization in Belgium will be done using REDCap (electronic IVRS system).

6.3 Study Schedule

The scheduled assessments will be carried out during the study as described in Section 9.4 of the Study Protocol.

6.4 Duration of Treatment and Study

The total treatment duration of the study is 5 days, followed by possible 5 day extension upon deterioration. The entire study duration is 10-22 weeks to final follow up visit.

6.5 End of Study Definition

The subject has completed the study if he or she has completed all phases of the study, including the last visit (week 10-20 clinical follow up visit) or the last scheduled procedures (refer to protocol section “9. Study Specific Procedures”).

6.6 Study Drug Administration

Refer to Sections 8 and 9.2 of the Study Protocol.

6.7 Study Assessments

6.7.1 Safety Evaluations

The safety and tolerability of study drug in each dosing cohort will be evaluated through:

- Incidence of AEs/SAEs.
- Pulmonary function tests
- Laboratory tests
- Physical examination
- ECG
- Chest X-ray
- Vital signs (including height and weight)

Adverse events (AEs) will be collected from the signing of informed consent form (ICF) to last subject contact/visit/end of post-treatment follow-up period.

Clinical exam, pulmonary function tests (including FVC, TLC and diffusion capacity), and a laboratory test (ferritin, lymphocytes, leukocytes) will be performed on routine check-up by pulmonologist at 10-20 weeks after discharge from hospital. Safety data, including blood leukocyte counts, will be collected in all patients.

Physical examination and vital signs will be tested from screening to last subject contact/visit/end of post-treatment follow-up period.

ECG and chest X-ray will be collected on clinical ground.

Refer to study protocol section 9.4 for the detailed schematic overview of the data collection & interventions.

6.7.2 Efficacy Evaluations

To measure the effectiveness of sargramostim on restoring lung homeostasis, the primary endpoint of this intervention is measuring oxygenation after 5 DAYS of inhaled (and intravenous) treatment through assessment of pretreatment (day 0) and post-treatment (day 5) ratio of PaO₂/FiO₂ and through measurement of the P(A-a)O₂ gradient.

The post-treatment evaluations should be assessed within 24 hours of the last dose of treatment. That is, Day 6 will be the timepoint for measures of efficacy endpoints based on 5 days of treatment, and Day 10 for patients who complete 10 days of treatment. If the patient is discharged from hospital prior to the day 6 (or day 10) efficacy evaluations, the values at day of discharge will be used as value for measuring efficacy endpoints.

Efficacy data will also be collected and will include arterial blood gases, oxygenation parameters, need for ventilation, lung compliance, organ function, radiographic changes, ferritin levels, triglyceride levels, etc. as well as occurrence of secondary bacterial infections.

7 Statistical Analysis Methods

7.1 General Considerations

All safety analyses will be based on Safety Population; all efficacy analyses will be based on mITT population, unless otherwise specified. Some specific sensitivity analyses of efficacy may be based on ITT (for primary endpoints only).

All analyses will be considered as descriptive analyses. Derivation of two-sided 95% confidence intervals and p-values will be generated where applicable.

Time to event endpoints will be defined as the start date/time to the end date/time; censoring dates will be the last date/time the patient was determined to be event-free. Kaplan Meier methods will be used for time to event endpoint analyses; a log-rank test will be performed to compare the two survival curves. Timepoints estimates and median survival will be derived from the Kaplan Meier analysis. A Cox proportional hazards model may also be used to compare the treatment groups using a hazard ratio.

Categorical endpoints will be calculated as the percentage of patients with the event, relative to the number of patients treated. Logistic regression approaches and/or repeated measures statistical approaches may be used to compare patients on the sargramostim and control arms, in addition to Fisher's Exact or Chi2 tests (as appropriate).

Continuous endpoints will be summarized by n, means, medians, minimum, maximum, and 25th and 75th percentiles. F-test and two sample t-test may be used to compare patients on the sargramostim and control arms.

In the event that the underlying assumptions and/or distributions for a given statistical method are not satisfied, alternative statistical methods will be employed.

Additional exploratory analyses may be performed to evaluate the robustness and sensitivity of the study results, including but not limited to the analysis populations, subgroup analyses, treatment interactions, adjusted or stratified analyses, and/or alternative statistical methods.

7.1.1 Study Day

Study day will be calculated as follows:

- For the sargramostim arm, first dose date is the first sargramostim dose date.
- For the control arm, the randomization date will be used as the first dose date.
- Assessments/events prior to the first dose date, study day will be the assessment date minus the first dose date. Assessments/events on or after the first dose date, study day will be the assessment date minus the first dose date plus one.

7.1.2 Baseline Definition

In general, the last observed measurement prior to the first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured, will be considered prior to the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The % change from baseline will be calculated as $(\text{post-baseline value} - \text{baseline value}) / \text{baseline value} \times 100$.

7.1.3 Analysis Period

The post-treatment evaluations should be assessed within 24 hours of the last dose of treatment. That is, Day 6 will be the timepoint for measures of efficacy endpoints based on 5 days of treatment, and Day 10 for patients who complete 10 days of treatment. If the patient is discharged from hospital prior to the day 6 (or day 10) efficacy evaluations, the values at day of discharge will be used as value for measuring efficacy endpoints.

The main analysis period would be the Treatment Emergent period which is defined as the period from the date of the first dose until the end of earliest of the following 1) the date of Day 28; or 2) Date of Early discontinuation from study. This analysis period will be used for all treatment emergent adverse event, laboratory evaluations and efficacy parameters.

For the primary endpoints, the data collected within first 6 days will be used for analysis.

7.1.4 Missing Data Handling

Missing data may be imputed using last-observation-carried forward, or other advanced statistical imputation methods for sensitivity analysis. For the primary endpoint, if assessments on Day 6 is not available, assessments on Day 5 will be used for analysis. If the patient leaves hospital prior to the day 6 analysis point, oxygenation at day of discharge will be used as value for measuring primary endpoint. Imputation for intubation rate and ordinal scale will not be performed.

When using last observation carried forward, a missing follow-up visit value will be imputed as that patient's previously observed value.

Regarding to time-to-event data, if no other specification in each section, the following rules will be used for missing data imputation:

- Patients who are not lost to followed up or experienced the event will be censored at the actual date of end of study visit.
- Patients who received no drug or standard of care will be excluded from analysis.
- Patients without an event but lost to follow-up will be censored at last date of follow-up.

7.2 Sample Size

The outcome(s) on which the sample size calculation is based upon, is the primary endpoint measurement of oxygenation, defined as ratio of PaO_2/FiO_2 and $P(A-a)O_2$.

Sample calculation and power analysis have been performed using Genstat. The target difference is the difference measured at the primary endpoint (at day 6) between the control and the treated group. Given a sample size of 40 patients each, a minimal improvement of 10% in the treated group relative to the control group will be detected as significant at a significance level of 0,01 with a power of 0.90. The error variance was set at 100 units, corresponding with a standard deviation of 10 units.

The post-treatment evaluations should be assessed within 24 hours of the last dose of treatment. That is, Day 6 will be the timepoint for measures of efficacy endpoints based on 5 days of treatment, and Day 10 for patients who complete 10 days of treatment. If the patient is discharged from hospital prior to the day 6 (or day 10) efficacy evaluations, the values at day of discharge will be used as value for measuring efficacy endpoints.

7.3 Data Safety Monitoring Board

Despite the known safety profile of the study medications and study design, a DSMB reviewed the data.

7.4 Analysis Population

The following analysis populations will be used to summarize the results from this study.

- **Safety Population** includes all patients who received at least one dose of sargramostim and/or SOC based on actual treatment received. Patients who did not receive any study treatment (either sargramostim and/or SOC) will be excluded from Safety Population. All safety analyses will be based on the Safety Population.
- **Intent-to-treat Population (ITT)** includes all patients who were randomized. Selected efficacy analysis (P(A-a)O₂) will be performed based on ITT population for the purpose of sensitivity, unless otherwise specified.
- **Modified Intent-to-treat Population (MITT)** includes all patients who were randomized and received at least one dose of sargramostim and/or standard of care based on the treatment assigned at randomization. All efficacy analysis will be performed based on modified ITT population, unless otherwise specified.
- **Enrolled Population** includes all patients who were eligible and signed informed consent form (ICF).

If the ITT is identical, or less than 10% different compared to the MITT population, then the selected efficacy analyses may not be repeated across the ITT analysis population.

7.5 Patient Disposition

Descriptive statistics by treatment will be used to summarize the number of patients screened, the number of screening failures, the number of patients enrolled, the number of patients in Safety Population, ITT, and mITT, number of patients who completed treatment period, completed the study, withdrawal from treatment, and withdrawal from the study, and reasons for withdrawals. The descriptive statistics will include numbers and percentages of patients in each identified category by treatment groups. A patient's data listing will be provided for disposition that includes patients who are excluded from the analysis populations; who prematurely withdrew from the study and reasons for excluding each analysis set, and for early discontinuation (from treatment and from the study).

For study completion status, the following logic will be used:

- Patient will be considered completed the study, if all of the following met: 1) complete the study treatment, 2) complete the first 5 study days, and 3) have a follow-up visit;
- Patient study completion status will be considered ongoing, if 1) patient started the study, and 2) the data cutoff date is less than 140 days away from the patient's first visit date in the Day 1-5 period;
- Patient will be considered discontinued from the treatment, if any of the following met: 1) the last date of drug taken is before Day 6 if the patients are in Group A, 2) the last date of drug taken is before Day 10 if the patients are in Group C/ D, 3) the last visit date is before Day 6 if the patients are in the control arm.
- Patient will be considered discontinued from the study, if any of the following met: 1) the patient is considered discontinued from the treatment, or 2) didn't complete the study treatment and the study status is not ongoing, or 3) didn't have a follow-up visit and the study status is not ongoing.

For withdrawal from study reason, the following logic will be used:

- If a patient was discharged before Day 6, the withdrawal from study reason would be "Discharged before Day 6";
- If a patient completed study treatment but did not have a follow-up visit, the withdrawal from study reason would be "Lost to follow-up";
- Else, the withdrawal from study reason would be the same as the withdrawal from treatment reason.

Patients will also be summarized by enrollment calendar time and treatment group.

7.6 Protocol Deviations

A subject listing of protocol deviations data will be presented.

The following general categories will be considered important deviations and be listed and discussed in the CSR as appropriate for the study:

- Deviation 1: Patients randomized but who did not receive study drug or standard of care
- Deviation 2: Patients who deviate from the following key entry criteria:
 - Inclusion:

- Exclusion:
 - Deviation 3: Patients randomized who received treatment other than that to which they were randomized to.

7.7 Demographics and Baseline Disease Characteristics

Demographic information for Safety Population will be summarized based on the first treatment that patients have received in the study. The demographic data consists of age, gender, race, ethnicity, along with baseline height, body weight, body mass index (BMI), Body Surface Area (BSA). The baseline the disease assessment scales, including the SOFA score (including categorization of <6 versus ≥ 6), ordinal scale, Hs Score, Clinical sign score, NEWS2 Score, CURB-65 score and APACHE II will be summarized.

Individual demographics and other baseline factors will be listed by patient.

Continuous variables (for example, age, height, body weight, body mass index, body surface area, disease assessment scales) will be summarized by n, means, medians, minimum, maximum, and 25th and 75th percentiles. Number of patients and percentages will be used to describe categorical (discrete) variables (for example, gender, race and ethnicity).

Individual demographics and baseline factors will be listed by patient.

7.8 Medical History

Medical condition and/or significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1, and listed by reported term, System Organ Class (SOC), and Preferred Term (PT). The number and percentage of patients will be summarized by SOC and PT by treatment group for Safety Population.

Baseline medical history will be summarized separately.

7.9 Concomitant Medications

All medications received after the consent to the study until the end of study will be coded using WHO Drug Enhanced Dictionary (WHODrug_20200901_B3) and categorized as Prior Medication, Concomitant Medication, or Post Medication based on the following:

- Prior medications include medications that have a start date and end date before the date/time of the first dose of the study treatment;
- Concomitant medications include medications that start date prior to, or after the date of first dose, that continues while the patient is on treatment (Day 10) and could continue on into follow up period;
- Post medications include medications that have a start date after the end date of the study treatment (Day 10).

Depending on the start and end date, a medication could be categorized as prior, concomitant, or post, or fall into more than 1 categories. For example, a medication with a start date prior to the first dose of study drug can be both prior and concomitant: if its end date is before the first dose of study drug, it would be prior medication; or it would be the concomitant medication only if the end date of the medication is after the first dose of the study drug.

Concomitant medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC) classes, and Preferred Term. Prior and Post Medications will be included in the patient's listing of medications including the start and end dates, prior/concomitant/post flag, whether it is ongoing, dose, unit and indication.

7.10 Extend of Exposure and Treatment Compliance

Treatment duration and treatment compliance will be summarized by treatment group. For each patient, the treatment duration is defined as the number of days from the first treatment date to the last treatment date, and can be calculated as:

$\text{Treatment Duration (Days)} = \text{Date of Last Treatment} - \text{Date of First Treatment} + 1.$

For the purpose of Day 1-5 treatment compliance though, the Date of Last treatment will be censored on Day 5 for patients who have taken sargoramostim beyond Day 5 (progressed and switched onto IV). For the overall treatment duration, the date of the last treatment will be either the date for the end of treatment record or the last treatment date in the database. For each patient the treatment compliance is defined as the actual treatment received as percentage of the planned treatment (K days). It can be calculated as:

$\text{Treatment Compliance} = 100 * (\text{Treatment Duration} - \text{Number of Days without Sargramostim within the period}) / K$

In these calculations, the study treatment would be sargramostim. The study specified treatment duration of sargramostim is 5 days. Therefore, $K = 5$, in general. For discontinued patients, K would be equal to the number of days from the date the sargramostim study drug is first received to the date of early discontinuation. For patients who received sargramostim after day 5 (e.g., groups C and D), these data will be presented in a separate treatment duration and compliance table. The compliance for standard of care will not be calculated or summarized.

7.11 Efficacy Evaluations

Key timepoints of interest for endpoints include Day 6 and Day 11, where data are available. All available efficacy data will be tabulated and presented for all patients in the mITT Population.

7.11.1 Oxygenation after 5 days of Sargramostim Intervention

To measure the effectiveness of sargramostim on restoring lung homeostasis, the primary endpoint of this intervention is measuring oxygenation after 5 days of inhaled (and intravenous) treatment through assessment of pretreatment and post-treatment ratio of $\text{PaO}_2/\text{FiO}_2$, $\text{SpO}_2/\text{FiO}_2$ and through measurement of the P(A-a)O_2 gradient. During the 5 day treatment period, daily measurements of oxygen saturation (pulse oximetry) in relation to FiO_2 will be performed. Negative value of P(A-a)O_2 gradient would be removed from the primary analysis.

P(A-a)O_2 gradient, $\text{PaO}_2/\text{FiO}_2$ ratio and $\text{SpO}_2/\text{FiO}_2$ are defined as:

$\text{P(A-a)O}_2 \text{ gradient} = [(\text{FiO}_2) \times (\text{Atmospheric Pressure} - \text{H}_2\text{O Pressure}) - (\text{PaCO}_2/0.8)] - \text{PaO}_2$

$\text{PaO}_2/\text{FiO}_2 = \text{Partial Pressure Oxygen} / \text{Fraction of Inspired Oxygen} * 100$

$\text{SpO}_2/\text{FiO}_2 = \text{Oxygen Saturation} / \text{Fraction of Inspired Oxygen} * 100$

Comparison will be between active group A receiving sargramostim on top of standard of care and control group B receiving standard of care. The change from baseline and daily change from baseline in oxygenation/respiratory parameter of P(A-a)O_2 gradient, ratio of $\text{PaO}_2/\text{FiO}_2$ and ratio of $\text{SpO}_2/\text{FiO}_2$ will be evaluated and summarized between group A and group B at Day 6. The difference of change from baseline between two groups will be tested by a t-test. In general,

the last observed measurement prior to the first dose of study treatment occurred on Day 1 visit will be considered the baseline measurement. Day 6 is the primary analysis point. If the patient leaves hospital prior to the day 6 analysis point, oxygenation at day of discharge will be used as value for measuring primary endpoint.

The analyses described above will also be performed between group A (early 5 day intervention with sargramostim) and group D (late 5 day intervention with sargramostim). Change from baseline (D1) to Day 10, daily change from baseline (D1) at Day 10 in oxygenation/respiratory parameter of $P(A-a)O_2$ gradient, ratio of PaO_2/FiO_2 and ratio of SpO_2/FiO_2 will be summarized as well. A t-test will be conducted to compare the difference between the groups.

The same analyses will be repeated for pathological oxygenation parameter of $P(A-a)O_2$ gradient, ratio of PaO_2/FiO_2 and ratio of SpO_2/FiO_2 including summary of their value and change from baseline at Day 6 and Day 10. A waterfall plot will be used to represent the change from baseline and percentage change from baseline on Day 6 for 1) oxygenation parameter of $P(A-a)O_2$ gradient; 2) pathological oxygenation parameter of $P(A-a)O_2$ gradient; 3) ratio of PaO_2/FiO_2 ; 4) ratio of SpO_2/FiO_2 . Percentage change from baseline of $P(A-a)O_2$ gradient and ratio of PaO_2/FiO_2 on Day 6 and follow-up will be summarized.

Reasons of missing AA gradient values on Day 6 will also be summarized.

The normal value of AA gradient for room air is calculated as: $2.5 + (0.21 \times \text{Age})$. All the results including change from baseline, and maximum change from baseline after 5 day intervention with sargramostim, normal AA gradient value for room air and flag of abnormality on Day 6 will be listed.

At least 33% reduction from baseline, and at least 50% reduction from baseline in $P(A-a)O_2$ gradient and pathological gradient on Day 6 will be summarized for mITT population.

Sensitivity analysis:

For the purpose of evaluating the sensitivity and robustness of the primary analysis using the mITT population, the above analyses will be repeated in the ITT Population.

7.11.2 Mean Change in Ordinal Scale Between Day 1 and Day 6

Ordinal scale will be assessed at the Screening and Days 1-10. Baseline for the following analyses is defined as the last ordinal scale prior to administration of study drug.

Ordinal Score at screening, day 1, day 6 and mean change between day 1 and day 6 will be summarized and listed between group A and group B.

7.11.3 Effects on Progression to Mechanical Ventilation and/or ARDS

Decreasing oxygenation often leads to the need for non-invasive or invasive mechanical ventilation, and if severe enough to a diagnosis of ARDS. We will therefore as a secondary endpoint also study if early intervention with inhaled sargramostim prevents progression to criteria-defined ARDS (according to the American-European Consensus Conference (AECC) diagnostic criteria for ARDS: acute onset; ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂) of 200 or less, regardless of positive end-expiratory pressure; bilateral infiltrates seen on frontal chest radiograph; and pulmonary artery wedge pressure of 18 mm Hg or less when measured, or no clinical evidence of left atrial hypertension), requiring high-flow oxygen devices, non-invasive mechanical ventilation, mechanical ventilation, by measuring the day from admission when this diagnosis is made or therapies are initiated.

Respiratory support includes high-flow oxygen devices, non-invasive mechanical ventilation, mechanical ventilation. The durations of respiratory support (days) are defined as:

Duration of respiratory support

$$= \sum_{k_i=0}^{N_i} (\text{End Date/time on Day } k_i - \text{Start Date/time on Day } k_i) / 24$$

Where, N_i is the total number of available study days for any patient i .

Number of patients with ARDS onset, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂), number of patients with bilateral infiltrates seen on frontal chest radiograph and duration of respiratory support will be summarized by treatment group.

Date of ARDS onset, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂), present of bilateral infiltrates seen on frontal chest radiograph and details regarding respiratory support will also be listed by patient.

Time to progression to invasive ventilation (days) is calculated as:

Time to invasive ventilation (Days) = Date of first invasive ventilation/Censoring– Date of randomization +1

All patients without progression to invasive ventilation during the study will be censored on the date of end of the follow up period, early discontinuation or death whichever is earlier.

The probability function of progression to invasive ventilation will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. Cumulative progression rates estimated by the KM method for day 6, 10, and available visits during the follow up period and the 95% confidence intervals will be reported.

7.11.4 Nosocomial Infections

As part of routine clinical care, sputum samples will be collected in patients suspected of secondary bacterial pneumonia, and checked for the presence of bacteria.

Identification / occurrence of nosocomial infections through the evaluation of BAL (bronchoalveolar lavage), sputum, skin, urine and blood culture results or other microbiology results, as well as adverse events, or via other medical procedures performed will be listed and summarized by treatment group using descriptive analyses.

Nosocomial infection rate per 1000 patient per day will be calculated as:

Nosocomial infection rate = total number of nosocomial infection cases / total number of hospitalization days for all patients * 1000

Wald test will be used to compare nosocomial infection rate between treatment groups.

7.11.5 Sequential Organ Failure Assessment (SOFA)

Overall calculated SOFA score will be summarized by treatment group for each available timepoint. Mean change of SOFA score between day 1 and day 6 and between day 1 and day 10 will be summarized by treatment group as well.

Individual GCS and SOFA scores will be provided in a patient data listing.

7.11.6 National Early Warning Score (NEWS-2)

National Early Warning Score (NEWS-2) in each available measure and the calculated overall NEWS-2 score will be summarized by treatment group for each available timepoint using descriptive analyses. Mean change of NEWS2 score between day 1 and day 6 and between day 1 and day 10 will be summarized by treatment group as well. Individual measures and overall score will be provided in patient data listing.

NEWS2 score less than 2 for at least 24h will be considered as an event.

Time to NEWS score<2 for at least 24h (days) is calculated as:

Time to NEWS score<2 (Days) = Date of first NEWS2 score<2 for at least 24h/Censoring– Date of randomization +1

All patients without achieving NEWS2 score less than 2 for at least 24h during the study will be censored on the date of end of the follow up period, early discontinuation or death whichever is earlier.

The probability function of progression to invasive ventilation will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. Cumulative progression rates estimated by the KM method for day 6, 10, and available visits during the follow up period and the 95% confidence intervals will be reported.

7.11.7 Clinical Sign Score

Clinical sign score ranges from 0-18 based on 6 parameters each scored 0-3 (by patient, except T°C). Overall clinical sign score and score on each parameter will be summarized by treatment group for each available timepoint using descriptive analyses. Mean change of clinical sign score

between day 1 and day 6 will be summarized by treatment group as well. Individual overall clinical sign score and score on each parameter will be provided in patient data listing.

Clinical sign score less than 6 maintained for 24h will be considered as an event.

Time to clinical sign score < 6 maintained for 24h (days) is calculated as:

Time to clinical sign score < 6 (Days) = Date of first clinical sign score < 6 maintained for 24h/Censoring – Date of randomization +1

All patients without achieving clinical sign score less than 6 maintained for 24h during the study will be censored on the date of end of the follow up period, early discontinuation or death whichever is earlier.

The probability function of progression to invasive ventilation will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. Cumulative progression rates estimated by the KM method for day 6, 10, and available visits during the follow up period and the 95% confidence intervals will be reported.

7.11.8 Mortality

Survival status will be collected up to follow-up period (20 weeks after day 1). Death is considered as an event. All the mortality events and cause of death will be listed by treatment group and by patient. Number of patients died and survival time will be summarized by treatment group. Survival time will also be listed by patient. Risk and risk difference of all causes mortality by Day 28 and during the study period will also be summarized.

The hazard ratio will be estimated by the Cox proportional hazards model with treatment group as a covariate in the model. Relevant hazard rates, hazard ratio between treatment groups and associated p-values will be tabulated.

Survival Time (days) is calculated as:

Survival Time (Days) = Date of Death/Censoring - Date of randomization +1

It is defined as the number of days from the date of first dose of study drug to the date of death or censoring. For patients who did not have deaths within 140 days' follow up time, the date of

censoring is the earliest of the following (1) early study discontinuations; (2) end of 140 days after the first dose; (3) last record in the database for those who were lost to follow up.

The probability function of death will be estimated by Kaplan-Meier method. The median time and its 95% confidence interval for each group will be reported. Cumulative progression rates estimated by the KM method for day 6, 10, and available visits during the follow up period and the 95% confidence intervals will be reported.

7.11.9 Hospitalization

The duration of hospitalization (days) is defined as:

Duration of hospitalization (Days) = Date of Discharge – Date of Randomization + 1.

Duration of hospitalization will be listed for each patient, and summarized by treatment group.

The duration of ICU (days) is defined as:

Duration of ICU(Days) = Date of Discharge from ICU – Date of ICU Admission + 1.

Number of patients who ever went to ICU and went to ICU on or before Day 28, along with ICU stay duration will be summarized and listed.

7.11.10 Feature of Secondary Haemophagocytic

Features of secondary haemophagocytic lymphohistiocytosis is defined by Hs score including temperature, organomegaly, cytopenia, triglycerides, fibrinogen, ferritin, AST and known immunosuppression. Hs score will be summarized by treatment group for each available timepoint using descriptive analyses. Individual Hs score will be provided in patient data listing.

7.11.11 Favourable Effect on long term follow up

At 10-20 weeks after discharge from hospital, patients will be seen on routine check-up by pulmonologist, who will perform a clinical exam (cyanosis, crepitation's and rales, heart murmurs, peripheral edema), pulmonary function tests (including FVC, TLC and diffusion capacity), and a laboratory (ferritin, lymphocytes, leukocytes). All the results will be listed by patient.

7.12 Safety Evaluations

Safety assessments will include monitoring of vital signs, adverse events (AEs), clinical laboratory tests, 12-lead electrocardiograms (ECG) and physical examinations. The main analysis period would be the Treatment Emergent period which is defined as the period from the date of the first dose until the end of earliest of the following 1) Date of Study Day 6 if a patient was not enrolled to Group C or D, or Date of Study Day 10 if a patient was determined to be enrolled in next 5 day treatment period; or 2) Date of Early discontinuation from study. This analysis period will be used for all treatment emergent adverse event, laboratory evaluations.

Safety variables will be tabulated and presented for all patients in the Safety Population and Intent-to-treat Population.

7.12.1 Adverse Event

Refer to protocol section 13.1 to see the definitions of adverse event. All adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Adverse event will be categorized as prior events, treatment emergent adverse event, and post treatment adverse event:

- Prior Events includes all adverse event with a start date before the first dose of the study drug or date of on study treatment (for SOC arm) regardless of the end date.
- Treatment-emergent adverse events (TEAE) are defined as adverse events with a start date (or date of worsening) on or after the date of on-study treatment.

TEAE will be summarized by: 1) treatment group; 2) system organ classification (SOC) and preferred term (PT); 3) PT; 4) SOC, PT and the maximum severity.

Treatment-related TEAE, serious TEAE and treatment-related serious TEAE will be summarized by SOC and PT coded by the most current version of MedDRA dictionary, and the maximum severity. SAEs and deaths will be listed by patient.

The frequency of treatment-emergent serious adverse event (TESAEs) will be summarized by treatment group, SOC, and preferred term. Severity (using CTCAE) and relationship of TEAEs to treatment (sargramostim, sargramostim inhalation device or standard of care) will be based on the scales as recorded on eCRF (also refer to Section 13.1 of the Study Protocol for definitions).

If a patient experiences more than one TEAE within a preferred term, the patient will be counted only once in the calculation of incidence of TEAE within that preferred term. Similarly, if a patient experiences more than one TEAE within a SOC, the patient will be counted only once in the calculation of incidence of TEAE within that SOC. If a patient experiences more than one TEAE within a preferred term (or SOC), the occurrence with the highest severity will be used in the calculation of the incidence of TEAE within that preferred term (or SOC) by severity. If a patient experiences more than one TEAE within a preferred term (or SOC), the occurrence considered most closely related to study drug will be used in the calculation of the incidence of TEAE with that preferred term (or SOC) by relationship to study drug.

A data listing for all AEs will be provided with flags for TEAE, relatedness and CTCAE severity. AEs related to sargramostim treatment will be listed. Any serious AEs and deaths will be listed.

7.12.2 Laboratory data

Laboratory data, as performed and collected as part of SOC (see [Section 9 in the Study Protocol](#)), will be collected and include hemoglobin, WBC, Eosinophil count, lymphocyte count, CD4+, CD8+, TBC, ESR, CRP, Creatinine, AST, ALT, Bilirubin, LDH, Troponins, CKs, Ferritin, Fibrinogen, Triglycerides, beta-HCG, D-Dimers and so on.

Descriptive statistics for baseline value, actual value and change from baseline to each scheduled postbaseline visit will be provided by treatment group for clinical hematology, chemistry laboratory, and immune profiling (where available) tests. Baseline for these tests is defined as the last assessment prior to administration of study drug. Conventional Units will be used for reporting the laboratory test results.

Serum pregnancy test results will be listed. Values for any chemistry, hematology, and immune profiling values outside the clinical reference ranges will be flagged on the individual patient data listings.

7.12.3 Physical Examination

Physical examination findings will be listed by treatment group and patient.

7.12.4 Vital Signs

Vital signs (including temperature, respiratory rate, blood pressure and pulse) will be measured during the Screening visit, Treatment period, Post-treatment period (within 24hrs), Study period, End of study and Follow-up period.

Baseline for vital signs is defined as the last assessment prior to administration of study drug.

All vital sign data including unscheduled records will be listed. Unscheduled records will be excluded from the summary statistics. Vital sign data including baseline value, actual value, and change from baseline to each post-baseline visit will be summarized by treatment group and timepoint.

7.12.5 Electrocardiogram (ECG)

Electrocardiogram examination findings for ECGs will be listed by treatment group and patient for each ECG parameter.

7.12.6 Patient Profiles

Key lab parameters for patients with SAEs, discontinuation due to AE, and deaths will be presented in patient profiles, in which the demographics and treatment data will be included. Additional profiles may be generated for any identified suspected unexpected serious adverse reactions (SUSARs).

8 Data Presentation

8.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the table, such as, “None reported”.

9 Revision History

10 Reference